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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/981,289	10/15/2001	Bassil I. Dahiyat	A-68990-3/RFT/RMS/RMK	5268

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EXAMINER

SEHARASEYON, JEGATHEESAN

ART UNIT	PAPER NUMBER
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1647

21

DATE MAILED: 12/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/981,289

Applicant(s)

DAHIYAT ET AL.

Examiner

Jegatheesan Seharaseyon

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 19 August 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-3 and 13-28 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 28 is/are allowed.
- 6) ☒ Claim(s) 1-3, 13-15, 17 and 19-27 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s) _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

1. This office action is in response to the amendment and response filed on 8/19/03 in Paper No: 20. Claims 1-3 and 13-16 have amended. Claims 17-28 have been newly added. Thus, claims 1-3, 13-16 and 17-28 are pending.
2. The text of those sections of Title 35, U. S. Code not included in this action can be found in a prior Office action.

Claim Objections

3. Claim 25 is objected to because of the following informalities: It recites cancelled claims. Appropriate correction is required.
4. Applicant argues that the Office had indicated that the 35 USC 112, first paragraph rejections were withdrawn in response to the declaration. This is clearly is not the case because paragraph 6 clearly directed the Applicant to see paragraph 8 for the rejection. There is a spelling error on line 2 of paragraph 6 of Paper No: 18. It should have read that: "the declaration provided by Dr. Robert Hayes under 37 CFR 1.132 filed 2/10/03 is insufficient to overcome" and not "sufficient" as indicated in the previous Office Action (Paper No: 18).

Claim Rejections - 35 USC § 112, second paragraph, withdrawn

5. The rejection of claims 1-3 and 13-16 under 35 USC § 112 2nd paragraph for being vague and indefinite with respect to "non-naturally occurring" is withdrawn. Further, the rejection of claims 3, 14, 15 and 16 are withdrawn in view of Applicants amendments.

Claim Rejections - 35 USC § 112 1st paragraph, maintained

5. Applicant's amendments of 8/19/03 have necessitated the withdrawal of the rejection of claims 3, 13, 14 and 15 under 35 USC § 112 1st paragraph for lack of written description and enablement. However, claims 1, 2, 16, 17, 19-24 and 27 are rejected under 35 USC § 112 1st paragraph for lack of written description and enablement for reasons of record both in Paper Nos: 13 and 18. The claims 1, 2, 16, 17, 19-24 and 27 recite variant TNF- α protein that does not refer to any sequence. In addition, claims 19-24 also recite the species information of TNF- α protein. In the absence of the recitation of a specific sequence, the skilled artisan cannot envision the detailed chemical structure of the claimed polypeptides, regardless of the complexity or simplicity of the method of isolation.

In addition, with respect to the scope of enablement provision, Applicant again fails to provide any guidance regarding a specific sequence contemplated. Furthermore, detailed information regarding the structural and functional requirements of the disclosed protein is lacking because there is no sequence recited. The specification as filed does not sufficiently teach one of skill in the art how to make and/or use the full scope of the claimed variant TNF- α proteins. The amount of experimentation required to make and/or use the full scope of the claimed invention would require trial and error experimentation to determine the functional sequences. Given the breadth of claims 19-24 and 27-28 in light of the unpredictability of the art as determined by the lack of working examples and shown by the prior art of record, the level of skill of the artisan, and the lack of guidance provided in the instant specification, it would require undue

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experimentation for one of ordinary skill in the art to make and use the claimed invention.

Claim Rejections - 35 USC § 102, maintained

6. Claims 1-2 and 14-15 and 19 remain rejected under 35 USC § 102(b) as being anticipated by Banner et al. (U.S. Patent NO: 5, 597, 899) for reasons set forth in Paper Nos: 13 and 18. Applicant's arguments filed on 8/19/03 have been considered but are not persuasive. Applicant asserts that the Office has mischaracterized the Banner reference and claims that the reference does not suggest, teach or disclose exchange between the mutants and wild type TNF-alpha to form mixed trimers. As noted by the following evidentiary art of Shin et al. (U.S. Patent NO: 5, 773, 582), human TNF is known to exist as a trimer with 3-fold axis of symmetry (column 1, lines 64-67) in the art. In addition, this Shin et al. also teach TNF muteins that have altered biological activities (column 2, lines 10-24).

Applicants also assert that Banner et al. reference does not suggest, teach or disclose the concept of mixed trimers, that is 1:2 or 2:1 combinations of naturally occurring human TNF-alpha with the variants of the present invention (page: 6, 5th paragraph). However, these specific combinations of mixed trimers were not recited in the previously presented claims 1-3 and 13-16. Thus, Applicant is arguing limitations not present in the claims.

As stated previously, the Office relied on the Banner reference to teach the generation of the various TNF-alpha mutations with at least one amino acid substitution. This reference teaches the preparation of mutations at several different amino acid

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positions compared to the wild-type TNF- α , which has different binding affinity to p55-TNF receptor compared to p75 TNF receptor. Using standard molecular biology techniques (abstract). Amino acid substitutions have been made at 33, 34, 65, 67, 75, 143, 145 and 147, including the following changes: D143N, D143E, A145R and A145K (abstract and Tables I and II). It also teaches generation of multiple amino acid substitutions compared to wild-type TNF- α sequence, including at least 3 amino acid substitutions (columns 5 and 6). Although Banner et al. may not have appreciated the trimer formation itself nonetheless meets the limitations of the instant claims in the teaching of the generation of various amino acid mutations. The art teaches that active TNF - α is a trimer. Thus, the formation of mixed trimers is a consequence of generating the mutants described in the prior art because it is necessary to at least have two different forms of TNF - α to generate the mixed trimers. Despite the fact that applicants may have been the first to characterize the formation of mixed trimers, the formation of mixed trimers would inherently have occurred in the presence of the teachings of Bennett et al. mutants, which are similar to those of the instant invention.

Applicants also argue that not all variants could form trimers, exchange with naturally occurring human- TNF - α and/or inactivate receptor signaling, because it is not necessarily an inherent property of all TNF - α variants. The Office disagrees with this position. Further absolute certainty not required. More likely than not the active mutant will trimerize (otherwise it would not be active!). In the absence Applicant reciting variants that are capable of forming mixed trimers, exchange with naturally occurring human- TNF - α and/or inactivate receptor signaling the teaching of Banner et al. clearly

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anticipate the instant invention. Applicant also argues that the mixed trimer formation is *in vivo* (page: 6, last paragraph). However, this limitation that was not recited in the previously presented claims 1-3 and 13-16. Thus, Applicant is arguing limitations not present in the claims. Applicant asserts that the Banner reference teaches enhanced receptor binding specificity and activating the specific receptor signaling advantageous (page: 7, first paragraph). In addition, Applicant also states the claims of the instant invention do not want to activate receptor signaling. Although, the Banner reference teaches muteins with higher binding affinity and greater specificity for hp75-TNF-R (column 3, lines 1-5), it is silent on receptor signaling. Therefore, there is no teaching away from the instant invention as asserted by the Applicant (page: 7, second paragraph).

The Examiner also notes the decision in *Swinehart and Sfiligoj*, 169 USPQ 226, in which it was found that mere recitation of a newly discovered function or property, inherently possessed by things in prior art, does not cause claim drawn to those things to distinguish over prior art. Although the prior art did not necessarily appreciate the mechanism of the formation of the mixed trimers, it clearly teaches the same TNF-alpha mutants, as the rejected claims. Thus, claims 1-2 and 14-16, 18 and 19 remain rejected under 35 USC § 102 (b) as being anticipated by Banner et al. (U.S. Patent NO: 5, 597, 899).

7. New claim rejections necessitated by Applicants amendments.

Claim Rejections - 35 USC § 112, second paragraph

8a. Claims 19-26 are rejected as vague and indefinite for not providing the species information of the TNF- α protein used in the instant invention. Numbering is not an inherent property, and without reference to a specific protein, is meaningless.

8b. Claim 21 is rejected as vague and indefinite for reciting the phrase "trimer comprises at least one different non-naturally occurring TNF- α proteins". It is unclear how one can have a single "different" protein, because it is not clear what this protein is different. TNF- α protein exists in nature as a trimer thus applicant clearly needs to indicate if the difference is in one of the monomer which is part of the trimer.

8c. Claim 27 is rejected as vague and indefinite for reciting the phrase "further comprises at least one amino acid sequence having at least one amino acid substitution as compared to the wild type TNF- α sequence". It is unclear how it is determined that the amino acid substitution contains a non-natural amino acid.

8d. Claims 19-24 are rejected as vague and indefinite because Applicant does not recite a wild type species for TNF- α protein.

9. Claim 28 is allowable.

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

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extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

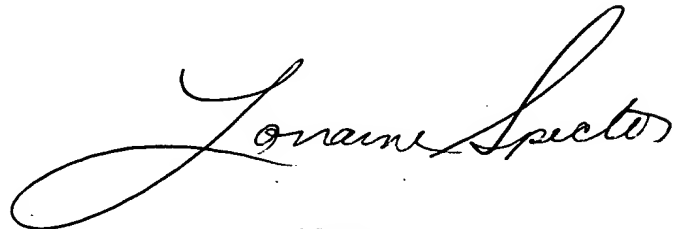
Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jegatheesan Seharaseyon whose telephone number is 703-305-1112. The examiner can normally be reached on M-F: 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on 703-308-4623. The fax phone number for the organization where this application or proceeding is assigned is 703-308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

JS

A handwritten signature in cursive script, reading "Lorraine Spector". The signature is written in black ink and is positioned above the printed name and title.

**LORRAINE SPECTOR
PRIMARY EXAMINER**